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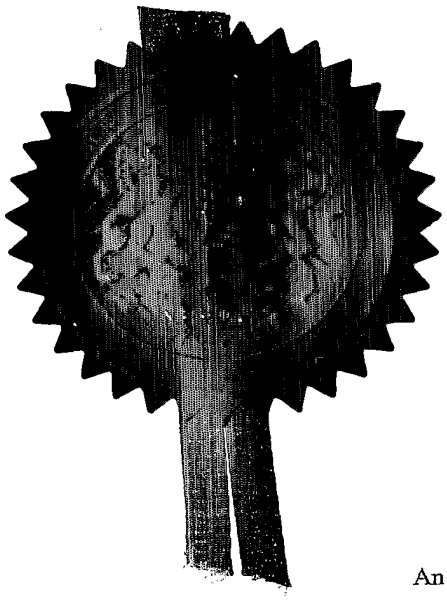

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P35985- /JDA/BOU

2. Patent application number
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10 FEB 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

The Queen's University of Belfast
University Road
Belfast
BT7 1NN
UK

Patents ADP number *(if you know it)*

81035170001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

"Method"

5. Name of your agent *(if you have one)*

Murgitroyd & Company

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Scotland House
165-169 Scotland Street
Glasgow
G5 8PL

Patents ADP number *(if you know it)*

1198015

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
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c) any named applicant is a corporate body.
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Description	12
Claim *(s)*	-
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature Murgitroyd & Co Date 9/02/03

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Method

The present invention relates to a method of producing a bioabsorbable implantable substrate, a method of altering the rate of bioabsorbability of a least a portion of a bioabsorbable implantable substrate, and a bioabsorbable implantable substrate, having graded molecular weight distribution formed according to these methods.

The long-term goal of biomaterials research lies in tissue regeneration, not replacement. In 'tissue engineering' biocompatible structures can be used either to engineer *in-vitro* living cellular constructs for transplantation, or to temporarily support load and facilitate *in-vivo* mechanisms for tissue regeneration. The ideal material for these purposes should provide high strength initially, then gradually degrade, transferring mechanical loads to regenerating tissue. Typical surgical applications are in the repair of connective soft tissue, ligaments or tendons and hard tissue such as bone.

In applications where tissue only requires temporary support or fixation the use of bioabsorbable polymers is appropriate. Depending on the choice of material and processing conditions, bioabsorbable polymers may retain their tissue supporting properties for days, weeks or months. Advantages of these materials are firstly, reduced risk of long-term complications because stresses are eventually transferred to the healing tissue, and secondly, the avoidance of the necessity for a retrieval operation.

Current trends in orthopaedic practice and research suggest that the most important bioabsorbable polymers used in surgery are synthetic polymers such as aliphatic polyesters (e.g. polyglycolide (PGA), polylactide (PLA) and their copolymers). These polyesters degrade *in-vivo* by hydrolysis into lactic acid and glycolic acid, which are then incorporated in the tricarboxylic acid cycle and excreted. These types of polymer generally degrade by bulk erosion, as the rate at which water penetrates the material exceeds the rate at which chain scission (into water-soluble fragments) occurs within the polymer [Middleton, J.C., Tipton, A.J., Biomaterials, 2335-2346, 2000]. Degradation in the interior of the device may occur faster than on the surface due to autocatalysis. The implication of this is that the device remains as a space-filler long after the useful strength of the polymer has deteriorated. The ingrowth of natural tissue is

prevented, and a 'lactide-burst' of low pH material may be released when the surface of the implant is finally degraded which can damage surrounding cells and cause inflammation.

According to a first aspect of the present invention there is provided a method of producing a bioabsorbable, implantable substrate having a graded molecular weight distribution, comprising the steps of providing an implantable substrate and altering the molecular weight distribution of at least a portion of the implantable substrate by exposing that portion of the implantable substrate to electron beam irradiation.

Preferably at least a portion of the surface of the implantable substrate is exposed to electron beam irradiation. Suitably the molecular weight distribution of the entire surface or body of the implantable substrate is altered by exposing the entire surface of the implantable substrate to electron beam irradiation.

At least a portion of the implantable substrate may be exposed to electron beam irradiation for 0.1 to 100 seconds. The electron beam irradiation may suitably have an intensity of 0.1 to 10 MeV. Suitably the electron beam irradiation penetrates 0.1 to 20 mm from the surface of the implantable substrate.

Preferably the exposure to electron beam irradiation also causes sterilisation of the implantable substrate.

The method may comprise the step of exposing the implantable substrate to one or more doses of electron beam irradiation. Each dose of electron beam irradiation may be at a different intensity.

Suitably each dose of electron beam irradiation penetrates the implantable substrate to a different depth. The molecular weight distribution, and thus the rate of biodegradation of the implant is suitably different at different depths.

According to a second aspect, the present invention also provides a method of modifying the rate of bioabsorbability of at least a portion of a bioabsorbable, implantable substrate comprising the step of exposing that portion to electron beam irradiation.

According to a third aspect of the present invention there is provided a bioabsorbable, implantable substrate obtainable by either of the methods described above.

The implantable substrate formable according to the methods of the present invention may have a graded molecular weight distribution through at least a portion of its thickness from its surface

thickness to the complete thickness of the implantable substrate. The molecular weight distribution of the implantable substrate may be lower towards the surface, and thus the rate of bioabsorbability is higher towards the surface. The rate of bioabsorbability may be pre-determined and controlled by altering the molecular weight distribution of the implantable substrate. The initial strength and average strength during degradation of the implantable substrate of the present invention are therefore also predictable and controllable.

In one embodiment, the outer surface of the implantable substrate biodegrades initially and the load bearing strength of the substrate is retained from the core. The implantable substrate of the present invention thus allows the ingrowth of natural tissue, whilst still providing some structural support.

According to a fourth aspect of the present invention, there is provided a bioabsorbable implantable substrate comprising a bioabsorbable polymer having a graded molecular weight distribution through at least a portion of its thickness.

According to a fifth aspect of the present invention, there is provided a bioabsorbable implantable substrate having an outer surface and a core wherein the molecular weight distribution of

the implantable substrate is greater at the core than at the outer surface, and the core is less biabsorbable than the outer surface.

Preferably the bioabsorbable implantable substrate of the present invention is bioabsorbable at a predetermined rate.

Preferably the outer surface and the core of the bioabsorbable implantable substrate are formed from the same material.

In general the bioabsorbable implantable substrate is suitably formed from aliphatic polyesters such as polyglycolide (PGA), polycaprolactone, polylactide (PLA), poly(dioxanone) (PDO), poly(glycolide-co-trimethylene carbonate) (PGA-TMC), polyanhydrides and copolymers.

The molecular weight distribution of the substrate is dependent on the material of the implantable substrate, but suitably the molecular weight distribution of the outer surface of the implantable substrate is from 10,000 to 100,000 and the molecular weight distribution of the core of the implantable substrate is from 100,000 to 500,000. Preferably the molecular weight distribution of the implantable substrate changes gradually from the surface to the core.

The rate of absorption of the implantable substrate into the body is dependant upon the material of the

implantable substrate and the size of the implantable substrate, however, the rate of absorption of the implantable substrate of the present invention may preferably be pre-determined and controlled to suit its purpose and is usually dependent on the material forming the implantable substrate.

Preferably the implantable substrate is bioabsorbed within 20 to 365 days, more preferably 60 to 120 days.

The bioabsorbable implantable substrate of the present invention may comprise additives such as bioactive agents and drugs. The additives may be incorporated into the bioabsorbable polymer to enhance tissue regeneration or reduce implant-related infection. The rate of release of the additives is not necessarily linear, and is dependent upon the absorption rate of the polymers, but is typically released over 20 to 175 days. The bio-active agents are released in a controlled manner as the outer surface of the implantable substrate biodegrades, and later as the core biodegrades. As such, the bio-active agents may be released as and when required to enhance tissue remodelling.

Preferably the implantable substrate is an interference screw, suture anchor, bioresorbable polymer composite (which is suitably self-

reinforced), or a bioabsorbable scaffold for tissue regeneration and growth.

The implantable substrate may cultivate tissue *in-vivo* or *in-vitro*.

According to a sixth aspect of the present invention there is provided the use of the bioabsorbable implantable substrate hereinbefore described, in the repair or treatment of disorders of or damage to hard or soft tissue.

According to a seventh aspect of the present invention there is provided a method of treatment of a disorder of or damage to hard or soft tissue comprising the step of implanting the bioabsorbable implantable substrate as hereinbefore defined in a human or animal body.

There is also provided the bioabsorbable implantable substrate as hereinbefore defined for use in therapy.

Suitably the hard or soft tissue may be connective tissue, ligaments, tendons or bone.

The disorder may be any tissue defect or trauma including osteo or rheumatoid arthritis, osteoporosis, inflammatory, neoplastic, traumatic and infectious tissue conditions, syndromes characterised by chondrodysplasia, cartilege damage, fracture, ligament tears, hernia,

synovitis, systemic lupus erthematosus, or wounds, particularly those sustained during surgery.

The degradation rate of bioabsorbable polymers is at least partially dependent on their initial molecular weight. The higher the initial molecular weight the longer the bioabsorption time (if all other factors are kept similar). It is now well established that all these polymers degrade by essentially the same mechanism – hydrolytic scission of the ester bonds. The reaction is autocatalytic and follows pseudo first order reaction kinetics:

$$M_n = M_{n.0} e^{-kt},$$

$M_{n,0}$ = initial mol. wt., k = constant

Therefore if the initial molecular weight of a polymer is known, the degradation rate can be predicted. The decrease in strength with time is also predictable from the molecular weight, using the equation:

$$\sigma = \sigma_\infty - \frac{B}{M_n},$$

σ_∞ = initial strength, B = constant

The penetration depth for electron beam irradiation depends on the energy of the electrons used and the density of the absorbing material. Penetration depth can be predicted from the expression:

$$d = \frac{(0.524E - 0.1337)}{\rho}$$

d = depth, cm

E = electron energy, MeV

ρ = density, gcm^{-3}

The typical densities of polyesters such as PGA and PLLA are in the range 1.0-1.5 gcm^{-3}, therefore electron penetration depth for energies in the range 0.3 to 10 MeV would be approximately 0.2 mm to 40 mm. The energy of a 10 MeV electron beam accelerator can be reduced by the use of metallic shielding of various thicknesses.

The present invention will now be described by way of example only, with reference to the accompanying drawings in which;

Figure 1 is an illustration showing the known bioabsorption behaviour of an implantable substrate known in the art.

Figure 2 is an illustration showing the bioabsorption behaviour of an implantable substrate according to the present invention.

Figure 1 shows that upon implantation in a human or animal body an implantable substrate known in the art undergoes a loss in strength and mass across its entire cross-section. Known implantable substrates have an even molecular weight distribution across their thickness and so the core

and surface of known implantable substrates are bioabsorbed at approximately the same rate. The space occupied by known implantable substrates does not reduce until the known implant is almost entirely bioabsorbed.

After implantation for a prolonged period of time, known implantable substrates undergo fragmentation due to a loss in mass. The core of such an implantable substrate fragments before the surface which may result in a "lactide-burst" of low pH material which can damage surrounding cells and cause inflamation.

Figure 2 shows an implantable substrate according to the present invention, and shows how the implantable substrate is bioabsorbed upon implantation into a human or animal body. The implantable substrate of the present invention has a graded molecular weight distribution, wherein the surface of the implantable substrate has a lower molecular weight distribution than the core.

The surface of the implantable substrate is bioabsorbed at a faster rate than the core of the implantable substrate, such that the surface of the implantable substrate undergoes loss in strength before the core and the space occupied by the implantable substrate is reduced gradually, thus allowing greater tissue ingrowth into the space occupied by the implant.

The core of the implantable substrate may still fragment but is bioabsorbed after the surface of the implantable substrate. The space occupied by the implantable substrate is reduced gradually during bioabsorption, encouraging tissue ingrowth.

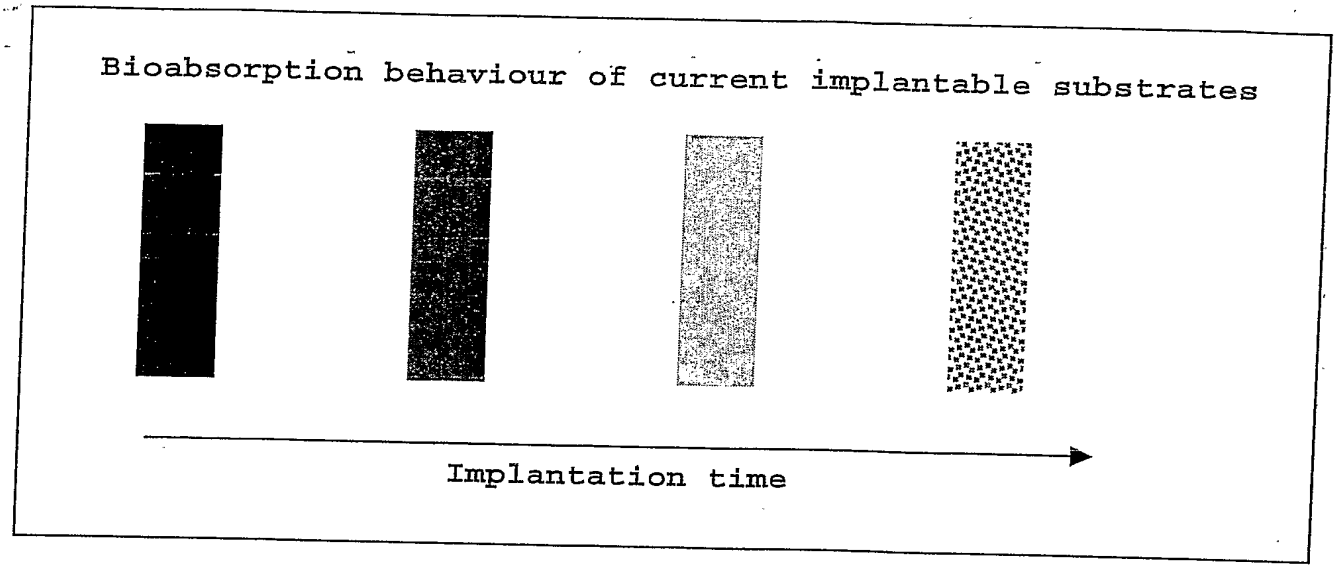

Figure 1

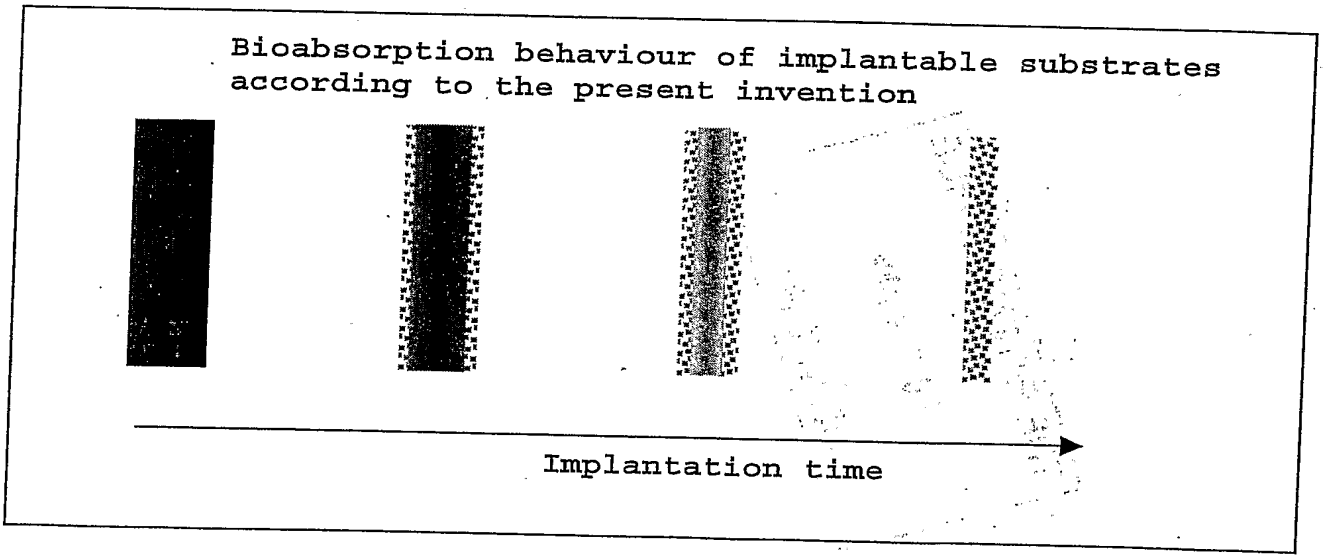

Figure 2